J Korean Med Sci 2000; 15: 289-94
ISSN 1011-8934

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Genetic Variation of the *Apo AI-CIII-AIV* Gene Cluster in Hypertriglyceridemic Patients with Chronic Renal Failure Undergoing Hemodialysis

Many patients with chronic renal failure (CRF) requiring hemodialysis present with hypertriglyceridemia (HTG). But the exact cause of HTG in CRF is still unknown. Genetic variation of the *apo AI-CIII-AIV* gene cluster was reported to be associated with primary HTG, atherosclerosis and coronary artery disease. This study was desiged to evaluate the association between the restriction fragment length polymorphism (RFLP) of the *apo AI-CIII-AIV* gene cluster and HTG in patients with CRF undergoing hemodialysis. Genetic variations of the *apo AI-CIII-AIV* gene cluster were analysed in peripheral leukocyte samples from 59 patients with CRF undergoing hemodialysis: 17 patients with HTG (CRF-HTG) and 42 patients without HTG (CRF-NTG). The RFLP was achieved through the digestion of PCR products by two restriction enzymes, *Sst*I and *Msp*I. The frequency of *Sst*I minor allele (S2) in CRF-HTG was 0.44, which was significantly higher than that in CRF-NTG (0.17). Frequencies of *Msp*I minor allele (M2) in CRF-HTG and CRF-NTG were not significantly different (0.5 vs 0.32) (p=0.07). Frequencies of S2-M2 genotype were 0.65 in CRF-HTG, and 0.27 in CRF-NTG (p<0.005). These data indicate that genetic variation of the *apo AI-CIII-AIV* gene cluster may serve as one of the causes of HTG in CRF.

Key Words: *Polymorphism, Restriction Fragment Length; Kidney Failure, Chronic; Hypertriglyceridemia; MspI; SstI*

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Received: 20 December 1999
Accepted: 24 February 2000

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INTRODUCTION

Dyslipoproteinemia is often associated with chronic renal failure (CRF). The most characteristic lipid abnormality is hypertriglyceridemia (HTG), regardless of the type of renal disease. Accelerated atherosclerosis is one of the major factors limiting the longevity of patients with CRF (1-6). The cause of HTG in CRF is unknown and current evidence favors the idea that HTG results from a decrease in the catabolism of very low density lipoprotein (VLDL), rather than an increase in their synthesis (3, 4, 7-9). A positive relationship appears to exist between the elevation of plasma triglyceride (TG) levels and the increased incidence of occlusive coronary artery disease, so the importance of HTG as a risk factor in coronary artery disease is re-emphasized (4, 10). Several studies have suggested association between restriction fragment length polymorphism (RFLP) of *apo AI-CIII-AIV* gene cluster, and HTG, atherosclerosis, coronary artery disease and myocardial infarction (11-15).

A polymorphic *Sst*I site in the apo C-III gene has been found to be associated with HTG (10, 16-18). The *Sst*I RFLP is proposed to be a marker of cardiovascular risk and to be helpful in identifying coronary prone individuals (12). S2 allele is in linkage disequilibrium with other allele in the *apo A-I, C-III, A-IV* gene cluster region, and S2-M2 alleles have also demonstrated strong linkage disequilibrium and are associated with HTG (11, 19-22).

Because HTG is observed in some CRF patients, and the duration of hemodialysis does not influence the level of TG, we postulated a possible association between genetic variation and HTG in patients with CRF. However, so far, the association between HTG in CRF and the genetic variation of the *apo AI-CIII-AIV* gene cluster needs further study. The aim of this study was to investigate the relationship between genetic variation at the *apo AI-CIII-AIV* gene cluster and HTG in CRF.

MATERIALS AND METHODS

Subjects

Fifty-nine patients with CRF were treated by chronic hemodialysis for more than 1 year in the St. Columban's Hospital, Mokpo, Korea. They consisted of 17 patients with TG greater than 150 mg/dL (CRF-HTG) and 42 patients with TG less than 150 mg/dL (CRF-NTG) (23-25). The underlying disease of 59 patients was hypertension in 14 patients, diabetes mellitus in 11 patients, polycystic kidney disease in 3 patients, glomerulonephritis in 4 patients, hypertension and diabetes mellitus in 3 patients and unknown disease in 24 patients. The control group was 56 individuals with TG less than 150 mg/dL who visited the health screening center at the same hospital, and was constituted so as to be similar to the CRF patient group with respect to age and gender. The CRF patients consisted of 35 males and 24 females. The control group was composed of 30 males and 26 females. The two groups did not differ significantly with respect to age (Table 1). The subjects were all Koreans.

Determination of plasma lipids and apolipoprotein

Blood was drawn from individuals who had fasted for 12 hr. Total cholesterol (TC) and TG were measured using the enzymatic method and HDL-cholesterol was determined by measuring the cholesterol in the supernatant liquid after precipitation of the plasma with $MgCl_2$ and dextran sulfate. Apo C-III was measured using the immunoturbidimetric method with commercial kits (Daiichi Co., Japan).

DNA analysis

Whole blood (6 mL) samples were mixed with EDTA to separate leukocytes. After washing leukocytes with phosphate buffered solution (PBS), they were stored in the 500 μL PBS at -70℃ until DNA extraction. The leukocyte stored tubes were centrifugated for 10 min, 5,000 *g*, washed with PBS and 400 μL of cell lysis buffer (0.32 M sucrose, 10 mM Tris HCl, pH 7.5, 5 mM $MgCl_2$, 1% Triton X-100), proteinase K (10 μg/100 μL lysis buffer) and 25 μL of 10% sodium dodesylsulfate (SDS) were added. This solution was incubated for 60 min at 60℃ and stored in ice for 3 min. Proteinase K was inactivated for 10 min at 95℃. A 2 μL sample of this supernatant was used as the template of PCR. To amplify the *apo C-III* 3'-untranslated region containing the polymorphic SstI site, the following primers were used: sense primer (5'-CAATTCGAAGGGTGATTCCT-ACCTTA-3') and antisense primer (5'-AAGCTTTTTGA-CTTGTGCTGGGGTTC-3'). Amplification was performed as previously described (5). PCR products were digested with *Sst*I endonuclease for 3 hr at 37℃ and electrophoresis was performed with a 3% agarose gel. S2 alleles were detected to have the *Sst*I cutting site in the amplified products. To analyze *Msp*I RFLP of the *apo AI-CIII* locus, genetic DNA was amplified using the following primers: sense primer (5'-CAGCGGCAGAGA-CTATGTGT-3') and antisense primer (5'-CGTTGTGC-AGCTGGACCGA-3') (19). The amplified products were digested with *Msp*I endonuclease for 4 hr at 37℃ and loaded at a 2% agarose gel. The *Msp*I cutting site was found to be absent in the M2 alleles.

Statistical analysis

The data were reported as mean±SD. Differences in lipid and apolipoprotein levels between controls and patients were analysed by one-way analysis of variance (ANOVA). Genotype distribution and allele frequencies were analyzed by Fisher's exact test. Chi-square analyses were used to compare combined genotypes distributions. Statistical significance was accepted at $p<0.05$.

RESULTS

Total cholesterol concentration in CRF-NTG patient group (144.3±33.8 mg/dL) was significantly different

Table 1. Clinical profiles (mean±SD) of subject groups

	No.	Age	Lipids			ApoC-III
			Total cholesterol	Triglyceride	HDL-C	
Control	56	48.6±8.1	177.6±21.8	96.8±31.3	46.2±9.0	7.1±2.0
CRF-NTG	42	52.1±10.1	144.3±33.8*	110.8±31.5	37.5±11.5*	13.6±6.4*
CRF-HTG	17	53.2±15.5	198.4±72.1†	279.1±107.4*,†	34.0±10.9*	20.1±7.0*,†

Age (year±SD), lipid (mg/dL±SD), apolipoprotein (mg/dL±SD)
HDL-C, high density lipoprotein cholesterol; ApoC-III, apolipoprotein C-III
*Significant difference between the patients and control subjects by ANOVA; $p<0.001$
†Significant difference between CRF-NTG and CRF-HTG groups by ANOVA; $p<0.001$

from that of the control group (177.6±21.8 mg/dL) ($p<0.001$). Triglyceride level was significantly higher in the CRF-HTG patient group (279.1±107.4 mg/dL) when compared with the level in the control group (96.8 ±31.3 mg/dL) ($p<0.001$). But it was not significantly different between CRF-NTG patient group and the control group. HDL-cholesterol concentration was significantly lower in both of CRF-NTG patient group (37.5± 11.5 mg/dL) and CRF-HTG patient group (34.0±10.9 mg/dL) than the control group (46.2±9.0 mg/dL) ($p<$ 0.001). The apo C-III value was significantly higher in all CRF patients than in the control group. In CRF-HTG patient group, the mean values of TC (198.4±72.1 vs 144.3±33.8 mg/dL), TG (279.1±107.4 vs 110.8±31.5 mg/dL) and apo C-III (20.1±7.0 vs 13.6±6.4 mg/dL) were higher than those in the CRF-NTG patient group ($p<0.001$) (Table 1).

Table 2 presents distribution of genotypes and allele frequencies for the *Sst*I and *Msp*I in all subject groups. The *Sst*I site showed significant association with HTG. The frequency of the S2 allele was not significantly different between CRF-HTG patient group and control group (0.44 vs 0.29) ($p=0.08$), but a higher frequency of the S2 allele was found in the CRF-HTG patient group compared with the CRF-NTG patient group (0.44 vs 0.17) ($p<0.005$). About 71% of CRF-HTG patient group were homozygotes or heterozygotes for the S2 allele compared with 45% of the control group ($p=0.06$) and 34% of CRF-NTG patient group ($p<0.01$). We can not find any significant M2 allele frequency difference between CRF-HTG and CRF-NTG patient group (0.5 vs 0.32) ($p=0.069$).

The distribution of combined genotypes of *apoC-III Sst*I site and *apoA-I Msp*I site in subject groups is shown in Table 3. In comparing the CRF-HTG group with the control group, there was a difference in the distribution of combined genotypes. And, especially between CRF-HTG and CRF-NTG patient groups, there was significant difference in the combined genotypes including S2-M2 haplotype as compared with genotypes excluding this haplotype ($p<0.01$).

The values of serum TG and apoC-III in different genotypes among the control group and CRF patients are given in Table 4. Although the TG concentration in the control group and patient groups were the highest in S2 and M2 homozygotes, any significant differences were not noted. But apo C-III values in the CRF patients were significantly higher in both the S2 and M2 homozygotes than the other S1 and M1 homozygotes and heterozygotes ($p<0.05$).

Table 2. Genotype distribution and allele frequencies for *Sst*I and *Msp*I polymorphisms in the subject groups

	No.	*Sst*I					*Msp*I				
		Genotype*			Allele frequency*,†		Genotype			Allele frequency	
		S1S1	S1S2	S2S2	S1	S2	M1M1	M1M2	M2M2	M1	M2
Control	56	0.55	0.32	0.13	0.71	0.29	0.43	0.43	0.14	0.64	0.36
CRF-NTG	42	0.66	0.34	0	0.83	0.17	0.41	0.55	0.05	0.68	0.32
CRF-HTG	17	0.29	0.53	0.18	0.56	0.44	0.24	0.53	0.24	0.50	0.50

*Significant difference between CRF-NTG and CRF-HTG groups by Fisher's exact test; $p<0.001$
†Relative risk between CRF-NTG and CRF-HTG groups; odds ratio 3.95 ($p<0.005$)

Table 3. Distribution of combined genotypes in the subject groups

	Control		CRF-NTG		CRG-HTG*	
	No.	Frequency	No.	Frequency	No.	Frequency
-(S2\M2)	31	0.55	31	0.73	6	0.35
S1S1M1M1	24		14		3	
S1S1M1M2	7		12		2	
S1S1M2M2	0		2		0	
S1S2M1M1	0		3		1	
+(S2\M2)	25	0.45	11	0.27	11	0.65
S1S2M1M2	17		11		7	
S1S2M2M2	1		0		1	
S2S2M2M2	7		0		3	
Total	56		42		17	

*Significant difference between CRF-NTG and CRF-HTG groups by Chi-square with continuity correction; $p<0.01$
Odds ratio 5.17

Table 4. Serum triglyceride (TG) and ApoC-III in different genotypes among subject groups

	S1S1	S1S2	S2S2	M1M1	M1M2	M2M2
TG (mean±SD, mg/dL)						
Control	89.3±28.1	104.0±32.8	111.6±35.9	86.8±29.1	104.0±29.6	105.1±37.9
CRF patients	145.0±100.7	172.0±100.0	219.0±33.2	154.4±93.5	159.3±109.5	176.3±61.7
CRF-NTG	109.2±32.4	114.0±30.3	-	119.3±35.3	104.7±27.3	108.5±45.9
CRF-HTG	345.6±121.6	262.2±104.8	219.0±33.2	303.5±122.6	298.9±118.1	210.3±32.2
Apo C-III (mean±SD, mg/dL)						
Control	6.8±2.0	7.5±2.2	7.2±2.0	6.8±1.8	7.3±2.3	7.2±1.9
CRF patients	14.1±6.1	15.9±7.5	26.5±7.7*	14.9±7.6	14.6±6.3	21.7±8.0†
CRF-NTG	13.1±5.6	14.6±7.9	-	14.5±7.6	12.8±5.8	13.8±1.7
CRF-HTG	20.0±6.3	18.0±6.6	26.5±7.7	16.8±8.6	19.0±5.7	25.7±6.5

*Significant difference compared S2 homozygote with S1 homozygote and heterozygote by ANOVA: $p<0.05$
†Significant difference compared M2 homozygote with M1 homozygote and heterozygote by ANOVA: $p<0.05$

DISCUSSION

HTG has been considered a well-recognized complication that occurs in CRF undergoing chronic hemodialysis treatment, but every patient taking hemodialysis treatment does not always present HTG (7, 9). The important causative factor of HTG in these patients is known decreased lipoprotein lipase (LPL) activity, although its definite action is unknown (3, 4, 7-9). It has been reported that the activity of LPL was decreased in the CRF-HTG but not in the CRF-NTG, and the duration of hemodialysis did not affect the TG concentration in the hemodialysis patients (6, 26). This may mean that HTG is not an absolutely concomitant phenomenon of renal failure, but it is related to the patient's genetic background. The most characteristic feature of the apolipoprotein profile in CRF is an early and marked elevation of the apo C-III level (7). The apo C-III may be an inhibitor of LPL, so there is a known positive relationship between the increase of TG and the elevation of apo C-III (27-29). Our data also presents a higher increase of apo C-III in CRF-HTG patient group than in the control group (Table 1).

Some studies have reported that there were several genetic variations in the *apo AI-CIII-AIV* cluster gene, and some of them were significantly associated with primary hypertriglyceridemia. The *Sst*I polymorphic site, more than any other site, is significantly associated with primary HTG, coronary artery disease, myocardiac infarction and atherosclerosis (11-15, 18). But there is no study about the association between HTG in CRF and the genetic variation of *apo AI-CIII-AIV* cluster gene.

The alleles of *Msp*I polymorphism at *apo A-I* gene and *Sst*I polymorphism at *apo C-III* 3' noncoding region showed large differences in frequency among the races, especially Caucasians and non-Caucasians (20). The frequencies of alleles of the M2 and S2 were 0.03 and 0.01 in Caucasians, but 0.37 and 0.35 in Japanese, 0.31 and 0.31 in Negroes and 0.36 and 0.29 in Koreans in this study. Despite wide differences in the various ethnic groups, S2 allele identified by a *Sst*I polymorphism in the *apo C-III* gene has still been found in higher frequency in subjects with primary HTG (15, 18-20).

Strong linkage disequilibrium of the S2 and M2 alleles has been demonstrated in Caucasians and non-Caucasian subjects and increased frequencies of the S2 and M2 alleles were found in hypertriglyceridemic patients. The S2-M2 haplotype was also more common in hypertriglyceridemic patients than normolipidemic patients (11, 19-21). So, these *apo C-III Sst*I and *apo A-I Msp*I sites may be useful genetic markers to predict individuals at risk for increased TG and perhaps also at risk for atherosclerosis (19). Our results slightly differ from those of the previous report by Zeng et al. (19). In the Zeng's study, the frequency of S2-M2 was significantly different at 0.42 and 0.7 in the control group and hypertriglyceridemic patients. But in the this study, the frequency of S2-M2 was 0.45 in the control group and 0.65 in the CRF-HTG patient group; they were not significantly different. Nevertheless there was a significant difference between CRF-HTG patient group (0.65) and CRF-NTG patient group (0.27). The frequency of S2 allele was 0.24 in the control group and 0.36 in HTG group in the study by Hong et al. (18), and 0.25 in the control group and 0.48 in HTG group in the study by Zeng et al. (19); they had significantly different results. But in this study, the frequency of S2 allele of the control group and CRF-HTG patient group was 0.29 and 0.44, although it appears to be a similar frequency compared with the previous study, it is not significantly different by statistical analysis. Moreover, it also identified significant differences between CRF-NTG patient group (0.17) and CRF-HTG patient group (0.44) in the frequency of S2 allele ($p<0.01$). These differences may be due to the fact

that different criteria were used in selecting subjects. In the previous studies, the TG concentrations of HTG patients were greater than 350 mg/dL and 240 mg/dL, but in our study they were greater than 150 mg/dL. In this sudy, there was a significant difference between CRF-NTG patient group and CRF-HTG patient group in the frequencies of S2 allele and in the distribution of S2-M2 genotype. This difference may help explain that there may be a genetic predisposition in HTG patients in CRF.

It is debatable that there is a direct relation between plasma apoC-III level and *Sst*I polymorphism in the *apo AI-CIII-AIV* gene cluster, because *Sst*I polymorphism site is in the noncoding exon region. But as there may be several linkage disequilibriums in the cluster, this site may involve increasing of apoC-III by collaborating with another effective gene. An increase of apoC-III is associated with increase of TG, but apoC-III increased more in both CRF-HTG and CRF-NTG patients than in the control group, even though the increase of apoC-III is higher in the CRF-HTG than in CRF-NTG patient group, as shown in this study (Table 1). As apoC-III-2 was a noncompetitive inhibitor of LPL, it may be a different apoC-III-2/total apoC-III in the CRF-NTG patients and CRF-HTG patients (27, 28). In this study, apoC-III in the S2 and M2 homozygotes was significantly higher than those in the S1 and M1 homozygotes and heterzygotes. This suggests that this genetic variation of the *Msp*I and *Sst*I sites may be one of the causative factors among multifactorial causes of apo C-III increase in CRF (Table 4).

Our study suggests that HTG observed in CRF patients undergoing hemodialysis may be associated with genetic variation of the *apo AI-CIII-AIV* cluster gene as reported previously in primary hypertriglyceridemic subjects.

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